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## The Use of Bone Age for Bone Mineral Density Interpretation in a Cohort of Pediatric Brain Tumor Patients

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### Abstract

**Background**—Skeletal bone accretion occurs throughout childhood. The integrity of this process may influence future adult bone health and risk for osteoporosis. Although surveillance of children who are at risk for poor bone accretion is important, the most appropriate method to monitor childhood bone health is not yet established. Previous investigators have proposed using bone age (BA) rather than chronologic age (CA) when interpreting bone mineral density (BMD) values in children.

**Objective**—To investigate the value of BA assessment for BMD measurement in a cohort of children at risk for poor accretion.

**Materials & Methods**—A cohort of 163 pediatric brain tumor patients who completed both a BMD assessment (quantitative computed tomography [QCT]) and a BA within 6 month interval was identified. The difference in BMD Z-scores determined by CA and BA was determined. The impact of salient clinical features was assessed.

**Results**—No significant difference between CA and BA Z-scores were detected in overall cohort (P-value=0.056). However, 18 patients (all male between the ages of 11 years and 15 years) were statistically determined to be outliers from the rest of the cohort.

**Conclusion**—Interpretation of BMD with BA measurement may be appropriate and impact treatment decisions in peri-pubertal males.

### Keywords

bone age; bone mineral density; children; quantitative computed tomography (QCT)

### INTRODUCTION

Bone fragility and its attendant risk for non-traumatic fracture—a condition commonly referred to as osteoporosis—is associated with significant morbidity and reduction in quality of life.[1, 2] Although several factors contribute to overall bone strength, bone mass or bone mineral density (BMD) is the primary determinant.[3,4] The process of bone accretion occurs

throughout childhood but accrual is maximum during the adolescent period.[5] Importantly, adult bone health may be negatively impacted if accrual of peak bone mass in adolescence is compromised.[6] Conversely, interventions designed to optimize peak bone accrual during this critical period may reduce the risk of future bone fragility.[1] Therefore, it is important to monitor children who are at risk for developing low BMD so that ameliorative interventions may be appropriately instituted.

In adults, BMD is typically measured by either dual-energy x-ray absorptiometry [DXA] or quantitative computed tomography [QCT]). Both methods generate a T-score (defined as the number of standard deviations (SD) above/below the average BMD value for young healthy women) that well correlates bone fragility and risk for fracture.[3] This score represents degree of bone loss since peak bone mass was achieved. Because children have yet to reach peak bone mass, Z-scores (defined as the number of SD above/below the average BMD for age-and gender-matched controls) are utilized rather than T-scores. Thus, pediatric patient values have been predominantly compared to normative populations that are age and gender matched.[7]

Unfortunately, because physiologic maturation rates may be disparate in same aged children, it is unclear whether chronological age (CA) used to generate Z-scores is the best predictor of actual physiologic bone status.[8] In children with abnormal physiologic maturation, the applicability of CA is even more uncertain.[9] Pediatric endocrinologists commonly use estimations of bone age (BA) in the clinical evaluation and monitoring of aberrant growth patterns. Because BA is presumed to better correlate with physiologic maturity, some investigators have proposed using this measurement rather than CA when interpreting BMD values in children.[9,10]

Utilizing a cohort of pediatric brain tumor patients at risk for or with known endocrinologic dysfunction, we investigated the value of BA assessment for BMD measurement in children. We hypothesized that CA and BA would differ to a significant degree in this cohort and that this difference would impact the interpretation of BMD.

## PATIENTS AND METHODS

After our institutional review board approved this study, an institutional database search annotated all patients who had undergone a QCT and BA analysis at St. Jude Children's Research Hospital for a variety of clinical indications between 10/2000 and 5/2006. Of these, 186 patients were identified as having a primary brain tumor. Because inclusion for analysis required that both exams be conducted within 6 months of each other, 23 patients were excluded. The final cohort was thus comprised of 163 patients. For patients with multiple examinations, the most recent data was used for analysis. Cohort demographic and diagnostic information was abstracted from an electronic medical record that is updated with each patient visit.

Initial tumor diagnosis was based on results of clinical, radiographic, and (when available) histopathologic analyses. The diagnosis was confirmed by review of the medical and pathology records and coded as one of the following: embryonal tumor, ependymoma, glioma, germ cell tumor (GCT), craniopharyngioma (CP), or choroid plexus carcinoma. Primitive neuroectodermal tumors (including medulloblastoma), pineoblastoma, and atypical teratoid/rhabdoid tumor comprised the embryonal group. Gliomas included neuronal/mixed neural-glial, astrocytic, and oligodendroglial tumors. On the basis of magnetic resonance imaging, we classified tumor location as optic nerve only, cerebrum (includes hemispheres and basal ganglia), diencephalon (includes optic chiasm/tract, hypothalamus, and thalamus), pineal, posterior fossa (includes brainstem and cerebellum), and spinal cord. With the exception of

optic nerve tumors, if the tumor overlapped more than one of the above regions, the site with predominant involvement was coded as the primary site.

The cohort's endocrine records were reviewed and conditions that may have contributed to aberrant patterns of growth or bone accretion were documented. Patients who lacked salient clinical signs, symptoms, or laboratory values suggesting hormonal dysfunction were presumed to have a normal endocrine status. Otherwise, specific diagnoses were based upon an assessment of clinical signs and symptoms, results of random or dynamic testing (spontaneous overnight secretion of thyroid stimulating hormone (TSH)[11], thyroid releasing hormone (TRH) stimulation[12], overnight Metyrapone testing[12,13], Insulin-induced hypoglycemia[14], low-dose adrenocorticotrophic hormone (ACTH) stimulation testing[12], Lupron stimulation testing[15], stimulation of growth hormone secretion with Arginine, L-dopa, Clonidine, or hypoglycemia), as well as, the intended outcomes of specific pharmacologic interventions.

*Precocious puberty* was coded for girls who experienced onset of puberty either before reaching a chronologic and/or bone age of 8 years or were  $\geq 8$  years at onset of puberty, but, because of concerns for undesired outcomes of final height and/or delayed cognitive-emotional capacity, their development was pharmacologically suppressed. In boys, precocious puberty was coded for those patients who experienced the onset of puberty before 9 years of age (chronologic and/or bone) or those that were  $\geq 9$  years at onset of puberty, but, because of concerns for undesired outcomes of final height and/or delayed cognitive-emotional capacity, their development was pharmacologically suppressed. An advanced bone age was not required to categorize patients with precocious puberty.

In patients that had the onset of puberty at a chronologic age or bone age that was older than the precocious categories, if their predicted heights decreased with advancing features of puberty, and the rate of changes in bone age maturation exceeded their change in chronologic age, the relative pace of these patients' puberty was frequently considered excessively rapid. These patients with rapid tempo puberty were often treated with luteinizing hormone-releasing hormone (LHRH) agonists to prolong their opportunity to grow. However, if patients had relatively rapid changes in pubertal development and advancement in bone age, but lacked decreasing or abnormally short predicted final heights and were not treated with LHRH agonists, they were categorized as rapid tempo of puberty without intervention. Additionally, in order to maximize benefit from GH therapy, some pubertal patients with documented or suspected GH deficiency and poor predicted heights were treated with LHRH agonists and categorized as pubertal suppression to maximize height. For analysis, all patients with evidence of precocious or rapid tempo puberty were considered together as *early-onset puberty*.

In this heterogeneous cohort, no single arbitrary chronologic age or bone age was consistently referenced in the clinical notes as differentiating excessively delayed puberty compared to stalled puberty or incomplete sexual maturation. If the clinical notes indicated that the intent of sex hormone therapy was to imitate a graduated progression of pubertal changes, the category of *delayed puberty* was applied. If the intent of sex hormone therapy was to simulate late adolescent or adult physiology, then the category of *hypogonadism* was applied.

In patients with a history of thyroid cancer or small thyroid nodules of indeterminate nature, administration of levothyroxine to produce some suppression of the TSH level was categorized as *purposeful TSH suppression*. For the purposes of categorizing the cohort, there was no differentiation of relative magnitude of TSH insufficiency. Thus, patients with evidence of partial or full TSH deficiency were labeled as *central hypothyroidism*. Patients with elevated levels of TSH were categorized as *primary hypothyroidism*.

Unless the preponderance of lab and clinical features supported ACTH deficiency, patients with a high index of suspicion for ACTH deficiency were not typically committed to maintenance therapy with glucocorticoids, but were advised to make use of stress dosing of glucocorticoids for any acute illness. In the analysis of this cohort, patients that only had recommendations for *stress dosing of glucocorticoids* were separated from patients on *daily maintenance glucocorticoid therapy*.

Clinical record review did not disclose a single absolute definition of growth hormone deficiency (GHD). If patients were treated with growth hormone for any length of time, they were categorized as *GHD, on treatment*. If growth hormone therapy was not utilized despite data to support GH deficiency, these patients were categorized as *GHD, off treatment*. Patients were categorized as having *multifactorial short stature* if they had past or present conditions associated with impaired growth, but did not have laboratory values to support GHD.

### Radiographic Technique

QCT of the lumbar spine was performed with a Siemens Somatom-Plus spiral CT scanner (Siemens, Iselin, NY) and Mindways QCT Calibration Phantoms and software (Mindways Software, Inc., South San Francisco, CA). BMD was determined by obtaining direct axial images of the first and second lumbar vertebrae (trabecular bone) as localized from a sagittal scout image. BMD ( $\text{mg}/\text{cm}^3$ ) was recorded for the individual bodies and the mean value was calculated. For BA measurement, a radiograph of the left hand and wrist was obtained and assessed using the method of Greulich and Pyle.[16] A total number of 4 readers, all CAQ (Certificate of Added Qualifications) Pediatric radiologists, were identified.

### Z-score Calculation

Z-scores based on chronological age (CA-QCT) were calculated by the manufacturer's software for each subject's BMD value (using the average values from L1-L2) as the number of standard deviations from the mean age- and gender-matched reference values provided by the manufacturers of the instruments. For comparison analysis of Z-score values based on BA analysis (BA-QCT), BA was substituted for CA using same gender-matched reference values provided by the manufacturers of the instruments.

### Statistical Methods

Analysis was conducted using SAS version 9 and Stat Xact 5. All continuous variables were tested for normality using the Shapiro-Wilk test. We tested for a significant difference between CA-QCT and BA-QCT using the Wilcoxon Signed Rank Test. A robust linear regression model was constructed using BA-QCT as the response variable and CA-QCT as a covariate. Robust linear regression identifies outliers and/or leverage points in the data and provides stable results in their presence.

Clinical and demographic variables (all were categorical) were tested for association with outlier status. For those variables which had two categories (ie. binary), Fisher's Exact test was used. For variables with more than two unordered (ie nominal) levels, this test was generalized to the Fisher-Freeman-Halton test. To account for the number of statistical tests performed in this analysis, we controlled the experiment-wise Type I error at the 0.05 level using the Bonferroni correction, which yielded a nominal level for significance of 0.003.

## RESULTS

### Cohort Characteristics

Cohort demographic, tumor, and radiation treatment information is presented in Table 1. The median age at diagnosis for primary brain tumor in this cohort was 4.2 years (0.3 to 14.0 years).

The median interval of years from diagnosis to first study (either BA or QCT, whichever came earliest) was 6.8 (1.1 to 17.0 years). The median age at time of first study was 13.1 years (3.2 to 19.1 years). Most patients were referred for BA by the division of endocrinology in the course of evaluation and monitoring of growth and puberty trends. QCT was typically obtained as part of a research protocol or after assessment with endocrinology.

### Comparison of CA-QCT and BA-QCT

The median chronological age at time of QCT was 13.1 years (3.3-19.1 years). The median BA was 13 years (3.0-17.0 years). The median CA-QCT Z-score was -1.21 (-4.57 to 2.12). The median BA-QCT Z-score was -1.20 (-4.62 to 2.00). Overall, no significant difference between CA-QCT and BA-QCT Z-scores were detected in this cohort (P-value=0.056). Furthermore, as expected, based on robust regression analysis, we found that these two methods of determining QCT Z-scores were significantly associated with one another (p-value < 0.0001, r-square= 0.74).

The relationship between CA-QCT and BA-QCT is illustrated in Figure 1a and 1b. Both depict a significant degree of association between these two tests. However, Figure 1a demonstrates several outliers (N=18) that were mathematically confirmed using robust regression technique.

### Analysis for Outliers

To better account for the difference noted in 18 patients when CA-QCT and BA-QCT is compared, further analyses using multiple demographic and clinical covariates were completed (Table 2). After applying the Bonferroni correction, only gender was found to be significantly associated with outlier status (P-value= < 0.0001; 100% of the outliers were male compared with 52% of the non-outliers).

### Change in QCT Z-score as a Function of Patient Age and Gender

Because BMD accrual is a maturational process that changes over time, we explored the potential influence of age and gender upon QCT measurement. Figures 2a and 2b depict the differences in Z-scores for male and female with respect to age at time of study. A higher degree of variance between CA-QCT and BA-QCT was noted in males between the ages of 11 and 15 years. Graphic side-by-side comparison of CA-QCT and BA-QCT by age is shown in Figures 3a and 3b. These boxplots are constructed by standard methods, with the bottom and top of the box representing the 1<sup>st</sup> quartile (25<sup>th</sup> percentile) and 3<sup>rd</sup> quartile (75<sup>th</sup> percentile), respectively. The line within the box represented the median, and the whiskers extend to the most extreme data points within  $1.5 \times$  interquartile range (IQR). Data points outside the whiskers are suspected outliers and are individually represented with a circle. Differences between the two studies are again observed in males between the ages of 11 and 15 years. Of note, the BA-QCT median Z-score, -0.9 (-3 to 0.6), is considerably less than the CA-QCT median Z-score, -0.2 (-1 to 0.8) in the 12-13 year old males. The BA-QCT median Z-score, -1 (-3 to -0.4), is greater than the CA-QCT median Z-score, -2 (-3 to -0.6), in 14-15 year old males.

## DISCUSSION

Bone health in pediatric brain tumor patients is affected by multiple factors including endocrine dysfunction,[17-19] previous irradiation,[20,21] exogenous steroid exposure,[22,23] limited mobility,[24-27] and chronic anticonvulsant use.[28,29] Consequently, as these patients age, many are diagnosed with BMD deficits.[30-33] Consistent with recommendations from the Children's Oncology Group[34], BMD assessments are routinely obtained at our institution in "at risk" patients. These results help to guide clinical practice including dietary advice and/or pharmaceutical intervention. Of note, our cohort's median CA-QCT Z-score was low (-1.21) but was within 2 standard deviations of normal.



Because interpretation of BMD is based upon a comparison of the subject's bone status with a reference population, the calculated Z-score reflects the degree of congruence or deviation from a mean value of BMD established in healthy children of the same chronological age. In this cohort of patients with primary brain tumors, we did not detect an overall statistically significant difference in Z-score whether measured by CA-QCT or BA-QCT (P-value=0.056). That is, in general, our findings do not support utilizing a bone age for adjusting BMD Z-score.

However, further inspection of our dataset revealed 18 patients (11%) who were mathematically determined to be outliers from the rest of the cohort, e.g., CA-QCT and BA-QCT were not well correlated in these patients. Interestingly, all of the outliers were determined to be male and primarily between the ages of 11 years and 15 years at the time of their evaluation. Other clinical and demographic covariates were not significantly associated (Table 2). The variance detected in CA-QCT and BA-QCT among peri-pubertal boys (Figures 2a and 3a) may reflect an increased physiologic rate of change in bone accretion that occurs during this period. Increased bone mineralization closely follows the rapid expansion of bone volume during the normal growth spurt in boys. Because the expected age of this critical period of mineralization is similar to the age seen in the outliers of our cohort, our data may suggest that the rate of bone accretion is changing such that a small difference in maturity (BA vs. CA) greatly impacts the expected BMD. Thus, similar to a previous report, the accuracy of a CA derived BMD in peri-pubertal males (healthy or not) is of concern[9] and may warrant adding BA adjustment to BMD evaluations for children exhibiting extremes of growth velocities.

Many of our patients had overlapping endocrine conditions that could have cumulative influences on skeletal growth and maturation. We expected some endocrine categories to have linkage with BMD trends. However, no covariate specific to endocrine conditions was found to be significantly associated with outlier status. In this regard, it is pertinent to note that, due to the highly selected nature of our cohort, the majority of our patients with hormonal dysfunction were receiving endocrine interventions that intended to normalize their growth and maturation. This could be expected to decrease the difference of CA from BA. Moreover, with regard to abnormal pubertal status which can affect bone maturation, all patients with known precocious puberty were under suppression and only a small percentage of our cohort (3%) had delayed-onset puberty. Therefore, we suspect that no association between outlier status and hormone status was detected because, in general, our patients with hypopituitarism were monitored and treated. Given this bias, our results may not be well generalized to all children at risk or diagnosed with hypopituitarism. Furthermore, our findings should not be considered representative of all pediatric brain tumor patients.

Other limitations and bias within this study must be disclosed. First, our data was generated by QCT and may not be applicable to the more commonly utilized application of DXA. Measurements from QCT were chosen for analysis in this study because QCT provides direct volumetric assessment of BMD which is believed to be important in BMD assessment in growing children[35-37] and because there is a relative dearth of information regarding the use of QCT in chronically ill children. Nonetheless, the selective nature of this sample may impart bias. Second, as discussed by others, our method of recalculation of Z-scores by substituting BA for CA has not been empirically validated because QCT reference data is based on CA, not BA.[9] In general, BA studies were requested for evaluation and monitoring of patients with obvious or potential aberrant growth patterns and therefore may evince selection bias. Although the interval between QCT and BA was no greater than 6 months, the elapsed time may have been sufficiently long to alter our results. BA interpretation was not centralized for this study and, thus, subjective determination may limit reliability. Finally, this study was retrospective in nature and, like all such studies, is subject to data collection limitations. In this regard, an inconsistent record prevented the analysis of other potentially important bone

altering factors like body mass, concomitant non-replacement glucocorticoid use, and dietary calcium or Vitamin D intake.

Given that our population consists of children treated for cancer, additional risk from exposure to radiation using QCT should be considered. At our institution, we estimate that the effective dose of radiation to a patient ranges from 0.63mSv -1.29 mSv per patient per study (depending on age 1-10y and mA of 50-100). Although this likely exceeds the estimated exposure received during DXA, it is considerably lower than many assume and can be justified by its judicious use in high risk patients. Furthermore, the radiation exposure using QCT is limited to the upper lumbar spine as opposed to that of DXA being the whole lumbar spine and often obtained in concert with a whole body exposure. QCT provides a direct volumetric measurement of BMD which, using DXA can be problematic in a growing child. An estimated volumetric measurement with DXA must be calculated which introduces error. The judicious use of QCT provides important information with regard to bone health in these medically complex children. Anecdotally, we have also found that because QCT is a technically faster study than DXA, it may be better tolerated in children with or altered delayed cognitive development and thereby obviate the need for sedation which has its own inherent risks.

In this study, utilizing QCT, we determined that BA may impact BMD measurement in peri-pubertal males. Furthermore, males aged 12-13 years had less bone accretion than suggested by CA-QCT and males aged 14-15 years had more bone accretion than suggested by CA-QCT. These findings are interesting and potentially could impact treatment decisions. Unfortunately, because no prospective, longitudinal measurements were available, the exact implications of these findings are unknown. A prospective study is currently being developed that would address whether BMD (measured by BA-QCT and CA-QCT) would change over time with respect to pubertal status or treatment/intervention. In addition, the relevance of BMD to fracture rate will also be assessed.

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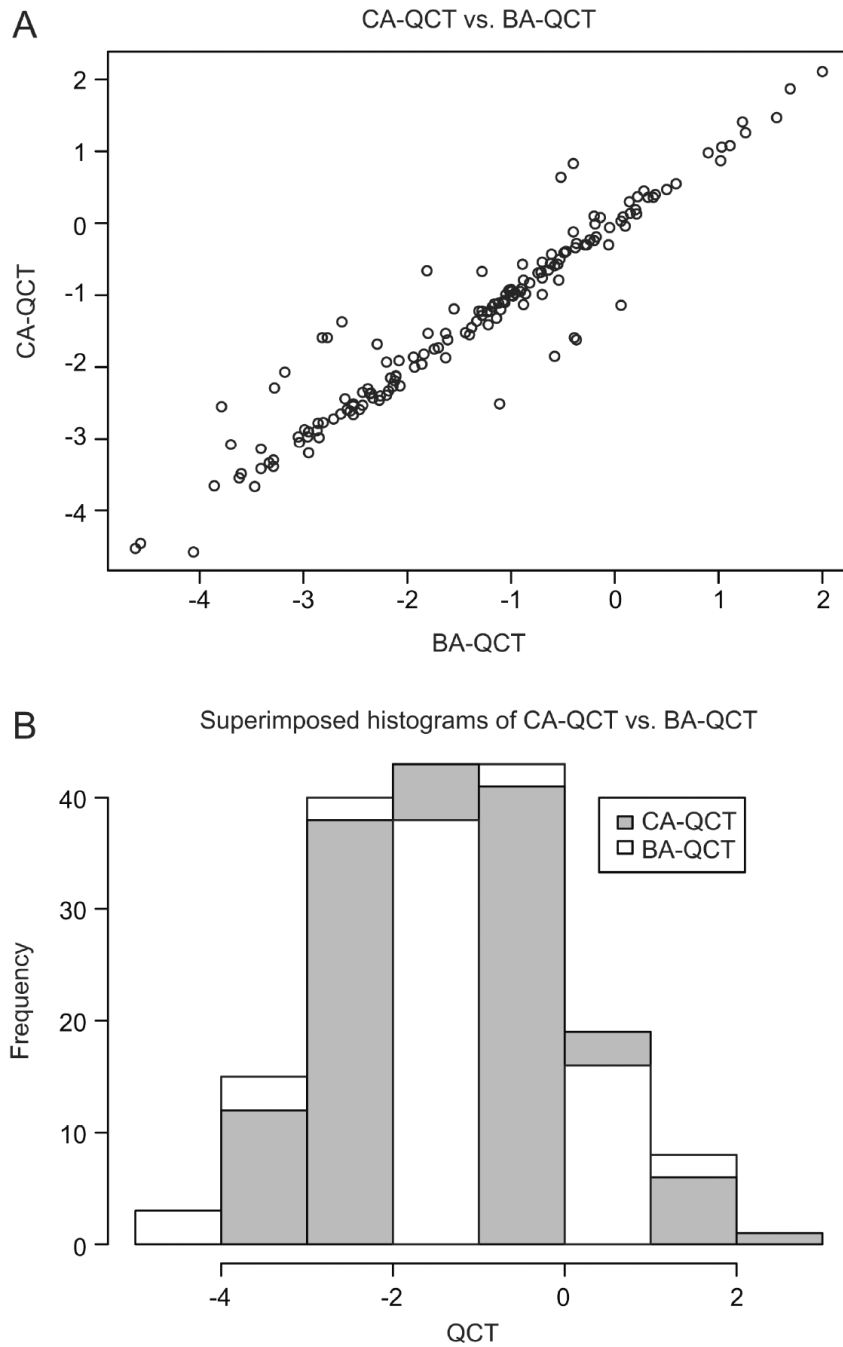
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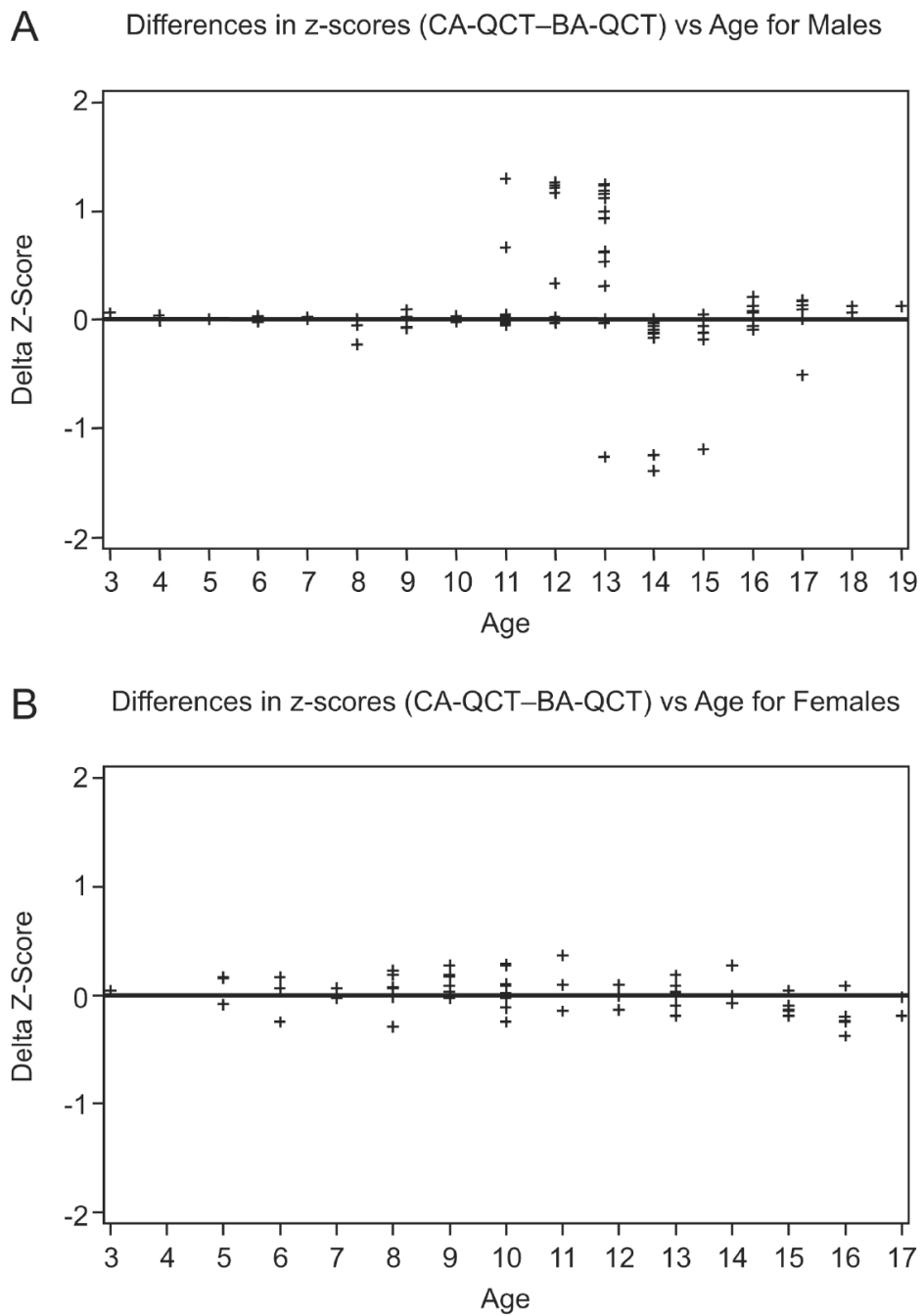
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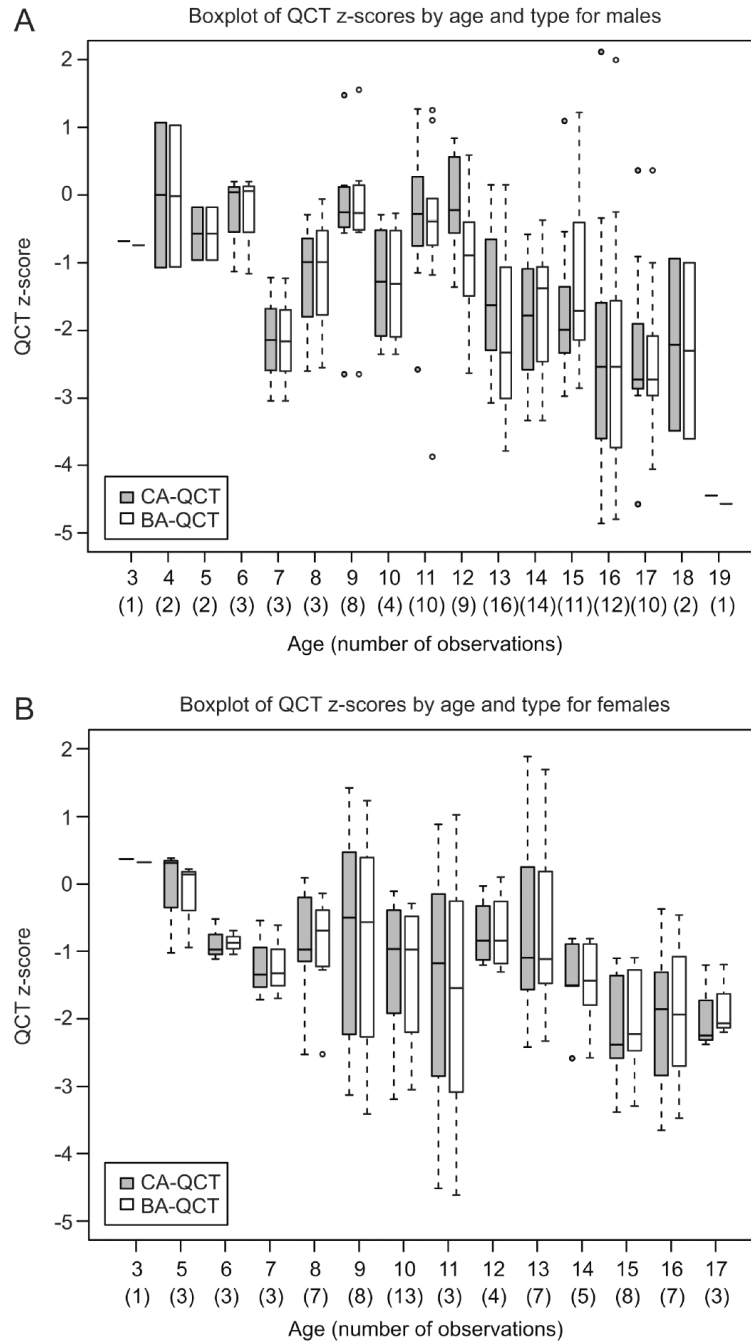
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**Figure 1.**  
 a: CA-QCT= quantitative computed tomography (QCT) z-score based on chronologic age of patient; BA-QCT= QCT z-score based on patient's bone age.  
 b: Comparison of the frequency of z-scores derived from both CA-QCT and BA-QCT



**Figure 2.**  
 a: Degree of correlation of CA-BCT and BA-QCT across ages in males  
 b: Degree of correlation of CA-BCT and BA-QCT across ages in females



**Figure 3.** a and b: Graphic side-by-side comparison of CA-QCT and BA-QCT by age and gender. The bottom and top of the box represent the 1<sup>st</sup> quartile (25<sup>th</sup> percentile) and 3<sup>rd</sup> quartile (75<sup>th</sup> percentile), respectively. The line within the box represents the median, and the whiskers extend to the most extreme data points within  $1.5 \times$  interquartile range (IQR). Data points outside the whiskers are suspected outliers and are individually represented with a circle.

**Table 1**  
Cohort Demographic and Clinical Information

		Male (N=93, 57%)	Female (N=70, 43%)	Total (%)
<b>Race</b>				
	White	71	60	131 (80%)
	Black	18	9	27 (17%)
	Other	4	1	5 (3%)
<b>Primary Diagnosis</b>				
	Embryonal Tumor	31	23	54 (33%)
	Ependymoma	12	15	27 (17%)
	Other Glioma	36	26	62 (38%)
	Craniopharyngioma/Germ Cell	12	6	18 (11%)
	Choroid Plexus Carcinoma	2	0	2 (1%)
<b>Primary Location</b>				
	Optic Nerve	0	2	2 (1%)
	Cerebrum	10	8	18 (11%)
	Diencephalon	29	19	48 (29%)
	Pineal	3	0	3 (2%)
	Posterior Fossa	51	40	91 (56%)
	Spinal Cord	0	1	1 (1%)
<b>Location of Radiation</b>				
	None	12	7	19 (12%)
	Cranial	45	38	83 (51%)
	Cranio-spinal	36	24	60 (36%)
	Spinal Only	0	1	1 (1%)
<b>Endocrine Categories*</b>				
	TSH Deficiency	56	37	93 (57%)
	Hypothyroid	8	6	14 (9%)
	GHD, on Treatment	58	37	95 (58%)
	GHD, off Treatment	2	2	4 (2%)
	Requires Daily and/or Stress HC	52	27	79 (48%)

\* Some patients are included in multiple categories



**Table 2**

## Variable Analysis of Outlier Status

Variable	P-Value
Gender	0.001
Race	1.00 <sup>*</sup>
Early-Onset Puberty	0.77
Delayed Puberty	0.09
Hypogonadism	0.31
Purposeful TSH Suppression	1.00
Central Hypothyroidism	1.00
Primary Hypothyroidism	0.66
Glucocorticoid, Maintenance	0.79
Glucocorticoid, Stress	0.49
GHD, on treatment	0.13
GHD, off treatment	1.00
Multifactorial Short Stature	1.00
Brain Tumor Type	0.44 <sup>*</sup>
Brain Tumor Location	0.97 <sup>*</sup>
RT (Yes/No)	0.04
RT (4 Groups)	0.08 <sup>*</sup>

\* P-Values for variance with more than 2 Groups are based on the Fisher-Freeman-Halton Test

RT= radiation treatment